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Original article

Prediction of atrial fibrillation after ischemic stroke using P-wave signal averaged electrocardiography

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ABSTRACT

Background: Atrial fibrillation (AF) is highly prevalent in patients with ischemic stroke, but the diagnosis is often difficult.
Methods: This study consisted of 68 stroke patients in sinus rhythm without history of AF. All patients underwent P-wave signal-averaged electrocardiography (P-SAECG), echocardiography, 24-h Holter monitoring, and measurement of plasma B-type natriuretic peptide (BNP) concentrations at admission.
Results: An abnormal P-SAECG was found in 34 of 68 stroke patients. In the follow-up period of 11 ± 4 months, AF developed in 17 patients (AF group). The remaining 51 patients were classified as the non-AF group. The prevalence of atrial late potentials (ALP) on P-SAECG, and the number of premature atrial contractions (PACs) were significantly higher in the AF group than those in the non-AF group (88.2% vs 37.3%; $p < 0.001$, 149 ± 120 vs 79 ± 69; $p = 0.030$, respectively). However, there were no significant differences in age, left atrial dimension, or BNP concentrations between both groups. Cox proportional hazards analysis revealed that the presence of ALP (risk ratio 11.15; $p = 0.002$) and frequent PACs (more than 100/24 h) (risk ratio 4.53; $p = 0.007$) had significant correlation to the occurrence of AF.
Conclusions: ALP may be a novel predictor of AF in stroke patients. P-SAECG should be considered in stroke of undetermined etiology.

1. Introduction

Atrial fibrillation (AF) is highly prevalent in patients with ischemic stroke. However, the diagnosis is often difficult because of its intermittent and frequently asymptomatic nature. In patients with a definite diagnosis of AF, oral anticoagulant therapy is recommended for prevention of recurrent stroke. On the basis of this recommendation, several approaches have been proposed for earlier detection of AF in stroke patients [1–3].

Signal averaged electrocardiography (SAECG) is a high-resolution electrocardiographic technique to detect conduction abnormalities in patients with structural heart disease. Impaired atrial conduction is one of the causes of AF, which was reported to be detectable by P-wave SAECG (P-SAECG) [4]. Previous studies using P-SAECG have shown that patients with abnormal P-SAECG have a high risk of AF [5,6]. The aim of this study was to investigate whether P-SAECG could predict the development of AF in patients with ischemic stroke.

2. Methods

2.1. Study population

This study is prospective and consisted of 68 consecutive patients with acute ischemic stroke presenting with sinus rhythm without a history of AF (31 females and 37 males, 69.9 ± 9.6 years). A history of AF was determined by the previous ECG and medical history. All patients were referred to Nippon Medical School Chiba Hokusoh Hospital between February 2006 and June 2011, and underwent 24-h Holter monitoring, P-SAECG, transthoracic echocardiography, and measurement of plasma B-type natriuretic peptide (BNP) concentrations within 5 days of admission. Patients were excluded if AF was documented in this term. Patients with known cardiac diseases or serious neurological sequelae were also excluded from the present investigation. The left atrial diameter (LAD) was measured at end systole in the parasternal long-axis view, and plasma BNP concentrations were determined with a specific immunoradiometric assay for human BNP with commercial

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kits (Shionoria kit; Shionogi and Kyowa Medex, Tokyo, Japan). From 24-h Holter monitoring, the number of premature atrial contractions (PACs) was calculated. The research protocol was approved by the local ethics committee and informed consent was obtained.

2.2. P-wave signal averaged electrocardiography

P-SAECG recordings were obtained from the Frank XYZ leads during sinus rhythm using a FDX-6521 (Fukuda Denshi Co. Ltd., Tokyo, Japan) in all the subjects. A total of 200 cycles were averaged with the P-wave triggering system to obtain a noise level of <0.4 μV. The signals were amplified and filtered with a band-pass filter at frequencies between 40 and 300 Hz. The filtered P wave duration (FPD) and the root-mean-square voltage for the last 20 ms (RMS20) of the signal-averaged P wave were measured. The algorithm of the P wave-triggering system of FDX-6521 was the same as that of VCM-3000 (Fukuda Denshi Co. Ltd.) [6]. Atrial late potentials (ALP) was defined as FPD > 132 ms and RMS20 < 2.3 mV [7].

2.3. Follow-up

All patients were followed up every 4 weeks after discharge, and examined with 12-lead ECG. 24-h Holter monitoring was repeated every three months after study entry. The primary endpoint was the development of AF, defined as irregular and uncoordinated atrial electrical activity on surface ECG lasting more than 30 s.

2.4. Statistical analysis

Data are expressed as mean ± standard deviation, and statistical analysis was performed by Mann–Whitney tests for unpaired variables. Categorical data were compared using chi-square analysis. AF-free rates in patients with and without ALP were calculated using the Kaplan–Meier method, and the difference between them was compared using the log-rank test. The determination of prognostic significance of ALP, Holter monitoring, echocardiogram, and plasma BNP level was explored by the multivariate Cox proportional hazards regression model analysis. A p-value < 0.05 was considered significant.

3. Results

In the follow-up period of 11 ± 4 months, paroxysmal AF developed in 17 patients (AF group). The remaining 51 patients were classified as the non-AF group. Notably, 7 (41.2%) AF patients were asymptomatic.

The AF group showed higher prevalence of ALP compared to that of the non-AF group (88.2% vs 37.3%, $p < 0.001$; Table 1). Representative cases of P-SAECG in both groups are shown in Fig. 1. Mean FPD and RMS_{20} in the AF group significantly differed from those in the non-AF group (FPD: 138.5 ± 8.6 vs 134.1 ± 8.3, $p = 0.047$; RMS_{20}: 1.73 ± 0.59 vs 2.8 ± 1.12, $p < 0.001$). The number of PACs on Holter monitoring was significantly higher in patients in the AF group than those in the non-AF group (149 ± 120 vs 79 ± 69; $p = 0.030$). While age and plasma BNP concentrations tended to be higher, LAD tended to be larger in the AF group than those in the non-AF group, they did not reach statistical significance. Cox proportional hazards analysis revealed that the presence of ALP (risk ratio 11.15; $p = 0.002$) and frequent PACs (more than 100/24 h) (risk ratio 4.53; $p = 0.007$) had significant correlation to the occurrence of AF (Table 2). Kaplan–Meier analysis showed that AF developed significantly more frequently in patients with than without ALP ($p = 0.0019$; Fig. 2). The ALP demonstrated a higher sensitivity and specificity for the identification of patients prone to AF compared to frequent PACs (88.2% vs 64.7%, 62.7% vs 52.9%, respectively).

Table 1
Comparison of each parameter in patients with and without AF development.

	AF group ($n = 17$)	Non-AF group ($n = 51$)	p-Value
Age (years)	73.5 ± 10.2	69.2 ± 9.5	0.064
Male	8	29	0.422
DM	4	6	0.254
HT	14	31	0.380
Smoker	5	9	0.315
FPD (ms)	138.5 ± 8.6	134.1 ± 8.3	0.047
RMS_{20} (μV)	1.73 ± 0.59	2.80 ± 1.12	<0.001
ALP	15	19	<0.001
PAC (betas/day)	149 ± 120	79 ± 69	0.030
LAD (mm)	40.9 ± 7.1	38.1 ± 5.7	0.063
BNP (pg/ml)	94.9 ± 55.3	73.6 ± 42.4	0.071

Data are given as the mean ± standard deviation or number of patients. AF, atrial fibrillation; ALP, atrial late potentials; BNP, brain natriuretic peptide.
DM, diabetes mellitis; FPD, filtered P wave duration; HT, hypertension; LAD, left atrial dimension; PAC, premature atrial contractions.
RMS_{20}, root mean square voltage of the terminal 20 ms.

Table 2
Multivariate Cox proportional hazard analysis for the identification of patients at risk for AF.

	p-Value	Hazard ratio (95% CI)
Age ≥ 70 (years)	0.188	2.06 (0.7–6.1)
ALP	0.002	11.15 (2.5–49.7)
PAC > 100 (beats/day)	0.007	4.53 (1.5–13.6)
LAD ≥ 41 (mm)	0.111	2.29 (0.8–6.3)
BNP ≥ 80 (pg/ml)	0.557	1.36 (0.5–3.8)

AF, atrial fibrillation; ALP, atrial late potentials; BNP, brain natriuretic peptide; CI, confidence interval; LAD, left atrial dimension; PAC, premature atrial contractions.

4. Discussion

Stroke patients who have AF are at high risk for recurrence, which can be reduced by anticoagulation therapy [8]. The second attack is often worse than the first, leading to serious sequelae or death. Therefore early diagnosis of AF is crucial, but may be overlooked when it is paroxysmal. Friberg et al. suggested that it is important to increase the use of anticoagulants among patients with paroxysmal AF because ischemic stroke is as common in paroxysmal AF as in permanent AF [9].

Identification of stroke patients who are prone to AF will allow for indication of anticoagulation therapy. Despite advances in diagnostic technique, early detection of paroxysmal AF in stroke

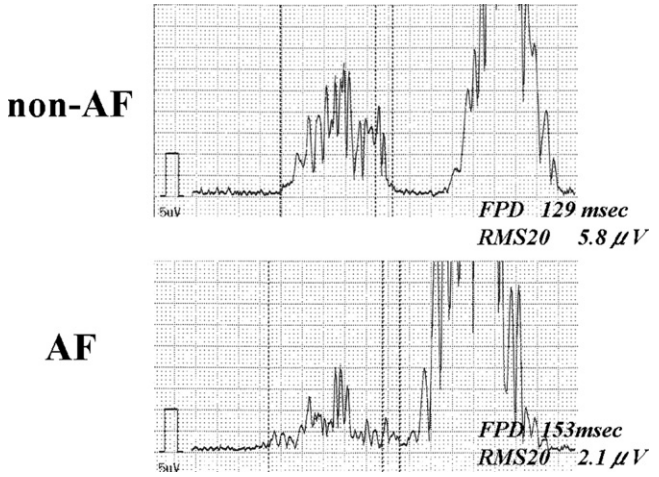

Fig. 1. Representative P-wave signal-averaged electrocardiography in each group. It is notable that the filtered P-wave duration (FPD) is longer and the root-mean-square voltage for the last 20 ms (RMS20) is lower in the atrial fibrillation (AF) patient than in the non-AF patient.

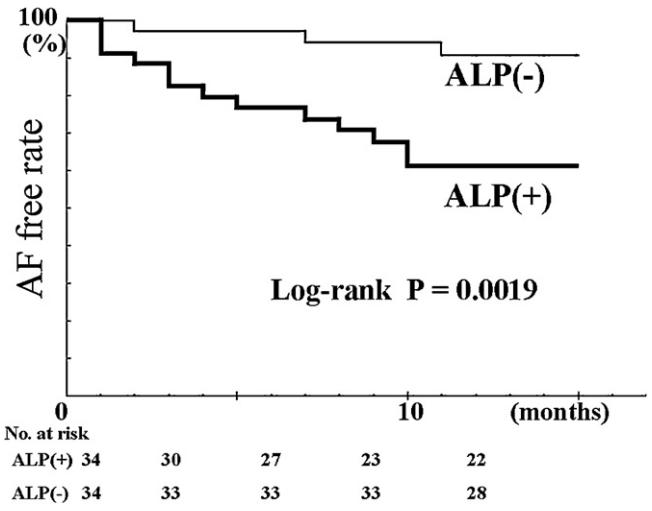

Fig. 2. The Kaplan–Meier primary atrial fibrillation (AF)-free curves for patients with and without atrial late potentials (ALP). The numbers at the bottom indicate the number of patients in each group at risk for AF. The AF-free rate was significantly lower in patients without than with ALP.

patients is still challenging. ALP detected by P-SAECG are thought to originate from areas of delayed and heterogenous conduction within the atrial myocardium, which are responsible for the occurrence of AF [4,5]. Previous studies have shown that P-SAECG is useful for identifying patients who are at risk for AF development after CABG [10–13]. Yamada et al. demonstrated the utility of P-SAECG for prediction of AF in patients with congestive heart failure [7]. Moreover, Ciçek et al. reported the predictive value of P-SAECG after acute myocardial infarction [14]. In the present study, we applied P-SAECG in stroke patients without clinical manifestation of AF. The prevalence of ALP on P-SAECG was significantly higher in the AF group than those in the non-AF group, and the AF group showed a significantly longer FPD and lower RMS_{20} compared to those in the non-AF group. Furthermore, multivariate analysis showed that the presence of ALP is independent and the most powerful predictor of AF.

AF is often initiated by PACs that originate in the ostia of the pulmonary veins [15]. Therefore frequent PACs on 24-h Holter monitoring are thought to be associated with the development of AF, and actually this has been demonstrated in stroke patients who are at risk for AF development [3].

In the present study, the number of PACs on Holter monitoring was significantly higher in patients in the AF group than those in the non-AF group, and multivariate analysis showed that frequent PACs is an independent predictor of AF development. These results are consistent with the previous findings, indicating that frequent PACs may be useful for detection of patients who are prone to AF.

The incidence of atrial fibrillation increases with age [16]. Although our results showed that age tended to be higher in the AF group than those in the non-AF group, it did not reach statistical significance. Age-related structural changes in the atria such as fibrosis may be associated with development of AF.

Left atrial size is an important factor in the development of AF [17,18]. In the present study, LAD tended to be larger in the AF group than those in the non-AF group, but it did not reach statistical significance. Recent studies have shown that left atrial volume is a superior predictor to LA diameter for development of AF. Further studies including left atrial volume will be needed because it may be a possible predictor for development of AF [18–20].

BNP is a hormone released mainly from the cardiac ventricles in response to myocardial wall stress, and associated with LV dysfunction in various cardiac conditions. Plasma BNP concentration is elevated in patients with paroxysmal AF, and maintenance of sinus rhythm can reduce BNP levels [21,22]. Recently, Tamura et al. showed that plasma BNP levels were markedly higher in patients with cardioembolic stroke compared to those with cryptogenic stroke [23]. The present study showed that plasma BNP concentrations tended to be higher in the AF group than those in the non-AF group, but it did not reach statistical significance. Hemodynamic change in acute phase of stroke may affect BNP levels. Tomita et al. suggested that elevated plasma BNP levels are increased in acute ischemic stroke independent of heart disease, and reflect the severity of stroke [24]. Furthermore, Nakagawa et al. reported that BNP levels are increased in stroke patients even in patients without AF, and they were correlated with mean arterial blood pressure on admission [25].

It is noteworthy that about 40% of AF patients are asymptomatic. This finding suggests that silent AF may be present before stroke attack. A recent trial has shown that patients who experience asymptomatic episodes of atrial tachycardia are prone to ischemic stroke [26].

4.1. Study limitations

The current study has some limitations. First, the number of patients is relatively small. Furthermore, our study population represented only 10% of the total ischemic stroke population ($n = 711$). There is potential bias because many of patients were excluded for aforementioned reasons. A prospective study in a larger number of patients is necessary to define the clinical implication. Second, there is not absolute proof that AF is a cause of stroke in our study. Stroke in patients with AF is not necessarily due to cardiogenic embolism, and other potential causes such as atheroesclerosis with large artery disease may exist. This is the most important limitation of the present study. Third, the detection rate of new-onset AF using routine Holter monitoring is limited, and silent AF episodes may be overlooked. In addition, the number of PACs on Holter monitoring is affected by spontaneous variability. Therefore long-term Holter monitoring may have been needed for improvement of diagnostic accuracy.

5. Conclusions

P-SAECG is useful to detect occult or silent AF. It should be considered in stroke of undetermined etiology.

Conflict of interest

None.

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